Inhibition of indoleamine 2,3-dioxygenase activity by fatty acids and prostaglandins: A structure function analysis

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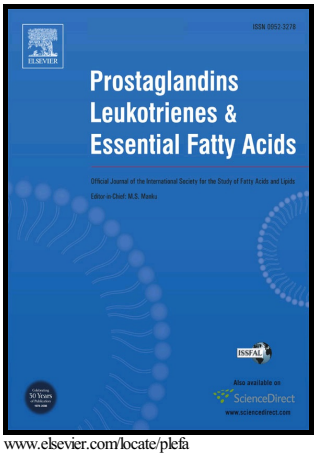

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Inhibition of indoleamine 2,3-dioxygenase activity by fatty acids and prostaglandins: A structure function analysis.

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Abstract

Indoleamine 2,3-dioxygenase-1 (IDO-1) catalyses the first and rate-limiting step in the metabolism of L-tryptophan. Degradation of L-Trp leads to the production of several immunosuppressive metabolites, including N-formyl kynurenine and kynurenine (Kyn). Apart from a normal physiological role, IDO-1 has also been identified to play a crucial role in immune suppression and tumour induced tolerance. Indeed, many primary tumours express high levels of IDO-1 compared to normal cells of the same stroma. IDO-1 is accepted as being an inducible negative regulator of T cell viability, proliferation and activation. As such, IDO-1 has become a target of intense interest for pharmacological inhibition, for the treatment of cancer. We have previously demonstrated that AA and the prostaglandin metabolite, PGD_2, repressed the IFNγ mediated activity of IDO-1 in THP-1 cells and human monocytes. In this study, we characterise the structure-function relationship of fatty acids and eicosanoids towards inhibition of IDO-1 activity in THP-1 cells and human monocytes. Using a commercial library of fatty acids, 55% of fatty acids inhibited IDO-1 activity. The

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